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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/853,641	05/14/2001	Madhavan Nampoothiri K.	32301WD1171	6478

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EXAMINER	
WALICKA, MALGORZATA A	
ART UNIT	**PAPER NUMBER**
1652	

DATE MAILED: 09/09/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/853,641	NAMPOOTHIRI K. ET AL.	
	Examiner	Art Unit	
	Malgorzata A. Walicka	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 July 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-24* is/are pending in the application.

4a) Of the above claim(s) *1-11,23 and 24* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *12-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *01/30/02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Response to Restriction Requirement filed July 30, 2004 is acknowledged. Claims 1-24 are pending; claims 12-22 are the subject of this office Action. Claims 1-11 and 23-24 are withdrawn from examiner's consideration as directed to the non-elected invention; see 37 CFR 1.142(b).

DETAILED OFFICE ACTION

1. Restriction/election

Applicant's election without traverse of Group III, claim 12-22, in the reply filed on July 30, 2004 is acknowledged. Applicants reserve the right to file divisional applications for the non-elected claims.

2. Objections

2.1. Priority

Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119 (a)-(d) or (f) as follows: Applicants claim foreign priority to the German Application 100 21 828.8 filed March 4. 2000, however certified copied of the priority documents have not been received.

2. 2. Specification

The specification is objected to because cross-reference to the parental application is not updated.

The specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicants' cooperation is requested in correcting any errors of which applicant may become aware.

2.3. Claims

Claim 16 is objected to as being not grammatical.

The word "simultaneously" should be deleted from preamble to claim 20.

Claim 22 is lacking the preposition "in" after the word "claimed" in the first line.

Claim 21 is objected to because genes cannot be fermented.

3. Rejections

3. 1. 35 U.S.C. 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claim 12-22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regard as the invention.

Claim 12 and 13 are confusing. Claim 12 is confusing in recitation "the cdsA gene or nucleotide sequences coding therefor is/are amplified."

1) A gene cannot be encoded, because it's the gene that encodes (a protein). Do Applicants intend to include the cdsA protein and cdsA gene in the claim?

2) If the gene product is to be included in the claim it cannot be amplified. It can be overexpressed. The gene itself, however, can be amplified, i.e. present in more that one copy in the genome and for that reason overexpressed or overexpressed by other mechanisms.

Claim 13 is confusing is reciting the phrase "the cdsA gene or nucleotide Sequences which code for it is amplified by being over-expressed." A gene cannot be encoded by polynucleotide sequences, because the gene consists of a polynucleotide sequence. The gene may also be represented in several forms (sequences) due to the degeneration of the genetic code or natural variants (alleles). The gene cannot be amplified by overexpression. The gene may be amplified, i.e. present in several copies in the cell. In result of amplification more than one copy of the gene is expressed, i.e., the gene is overexpressed in comparison with the normal situation when only one copy of the gene is present and expressed. Overexpression my take place also when one copy of the gene is present in the cell but natural or man-introduced mechanisms controlling expression allow for more efficient expression; see [10016] which quotes the relevant mechanisms.

Claims 17 is rejected because the claim recite "further genes in the biosynthetic pathway of the desired L amino acid" are enhanced. The claim is

unclear as to what L-amino acid is to be synthesized and what genes are to be enhanced.

Claim 18 is rejected for the recitation "at least partially suppressed". The term "at least partially" is a relative term, which renders the claim indefinite. The term "at least partially suppressed" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably appraised of the scope of the invention.

2.2. 35 U.S.C. 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2.2.1. Lack of written description

Claims 12 -22 are rejected under 35 U.S.C. 112,first paragraph, as containing subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The claims are directed to a method of amino acid production in a *Coryneform*

bacteria containing amplified or overexpressed cdsA gene encoding phosphatidate cytidylyl transferase. Thus, the claims are directed to a genus of methods of using coryneform bacteria comprising cdsA gene, of indogenous or exogenous origin, the structure of which is not sufficiently described by the specification. Applicants teach only one species of the genus, i.e., SEQ ID NO:

1. This information is, however, not sufficient to put in possession of one skilled in the art the attributes necessary to make the claimed invention. The specification fails to describe any other representative species of the polynucleotides encoding phosphatidate cytidylyl transferase by any dentifying characteristics or properties other to encode a phosphatidate cytidylyl transferase protein. Neither the claims nor the specification provide a structure or a common structural feature of the polynucleotides of the claimed methods. In view of lack of specific structural characteristics of these polynucleotides, the specification fails to sufficiently describe the claimed invention in such full, clear concise, and exact terms that a skilled artisan would recognize the inventors were in possession of the claimed invention at the time the instant application as filled.

In addition, claims 12-22 are directed to a method of production of L-amino acid by *Coryneform* bacteria wherein the gene that codes for phosphatidate cytidylyl transferase proteinand genes dapA, dapE, lysE, lysC, tpi, gap, pgk, pyc, mqo, LysE is **amplified by a large genus of methods**. Such methods have not been sufficiently described. Applicants did not teach how the C*oryneform* bacterium of the claimed invention was

transformed, so as to amplify, according to their definition, the cdsA gene. On page 3, paragraph [0014] and further in paragraphs [0015] and [0016] Applicants write,

"[0014] The term amplification describe the increase in the intracellular activity of one or more enzymes in a microorganism, which enzymes are coded by the corresponding DNA. [0015] Amplification may be achieved by means of various manipulations of the bacterial cells. [0016] Amplification, in particular overexpression, may be achieved by increasing the copy number of the corresponding genes, by using a strong promoter or by mutating the promoter and regulation region or the ribosome-binging site located upstream from the structural gene. Expression cassette incorporated upstream from the structural gene act in the same manner. It is additionally possible to increase expression during fermentative L-lysine production by means of inducible promoters. It is also possible to use a gene which encodes for a corresponding enzyme having an elevated activity. Expression is also improved by measures to extend the lifetime of the mRNA. An overall increase in enzyme activity is moreover achieved by preventing degradation of the enzyme."

The methods are enumerated as a theoretical possibility, because the specification fails to describe mutations that would achieve such amplification or how one could extend the lifetime of the mRNA or how one could prevent degrading the enzyme protein. The examiner concludes that Applicants failed to sufficiently describe the claimed invention in such full, clear concise, and exact

terms that a skilled artisan would recognize they were in possession of the claimed invention at the time the instant application was filled.

In addition, claim 22 is directed to the method of production of L-amino acids by *Coryneform* bacteria wherein the genes from the group consisting of the pck gene, pgi gene and poxB gene is/are simultaneously attenuated. The term attenuated refers to complete lack of activity of the encoded protein, which may be achieved by gene deletion, disruption, or a substitution or insertion of a nucleotide/nucleotides. The term "attenuated" also refers to decrease in gene expression or activity of the encoded protein that my be achieved by mutation in sequences controlling the expression or mutations in the sequences encoding the structure of the protein. Applicant do not teach how the attenuation of the genes was performed. The examiner concludes that Applicants failed to sufficiently describe the claimed invention in such full, clear concise, and exact terms that a skilled artisan would recognize they were in possession of the claimed invention at the time the instant application was filled.

Furthermore, claims 20-22 are rejected for lack of written description as directed to the method of production of L-amino acids by *Coryneform* wherein the bacteria include one of the following overexpressed/attenuated genes: dapA, dapE, lysE, lysC, tpi, gap, pgk, pyc, mqo, LysE, pck, pgi, poxB. The claims are directed to a large genus of methods in which several genes are to be overexpressed or attenuated. Said genes are representatives of larage genera of genes for which the representative species are described on page 12 of the

specification. The specification fails to teach other species of the genera, by giving their structural characteristics. Thus, the examiner concludes that Applicants failed to sufficiently describe the claimed invention in such full, clear concise, and exact terms that a skilled artisan would recognize they were in possession of the claimed invention at the time the instant application was filled.

Limiting the claims by quotating the origin and structure of said genes would overcome this rejection.

2.2.2. Scope of enablement

Claims 12-22 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of producing lysine by overexpressing the polypeptide of SEQ ID NO: 2 in *Coryneform* bacteria, does not reasonably provide enablement for methods of producing any amino acid by amplifying the cdsA gene, from any biologic or man made source, by any method. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. The claims are broader than the enablement provided by the disclosure with regard to the extremely large number of methods that are claimed in claim 10-17 as set forth above in the rejection for lack of written description. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Otherwise, undue experimentation is necessary to make

the claimed invention. Factors to be considered in determining whether undue experimentation is required, are summarized *In re* Wands [858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)].

The Wands factors are: (a) the nature of the invention, (b) the breadth of the claim, (c) the state of the prior art (d) the relative skill of those in the art, (e) the predictability of the art, (f) the presence or absence of working example, (g) the amount of direction or guidance presented, (h) the quantity of experimentation necessary.

The nature and breath of the claimed invention encompass methods of producing amino acid by amplifying any cdsA protein from any biologic or man-made source wherein the amplification is achieved by any method, for example by

(1) increasing the copy number of the corresponding genes,

(2) mutating the promoter and regulation region,

(3) mutating the ribosome–binding site located upstream from the structural gene,

(4) using an expression cassettes incorporated upstream from the structural gene,

(5) using inducible promoters,

(6) extending the lifetime of mRNA,

(7) preventing degradation of the enzyme protein or

(8) modifying the composition of the nutrient media and culture conditions.

While methods of gene isolation, gene structure manipulations and characterization of the protein encoded by the isolated gene are known in the relevant art, and skills of the artisans highly developed, it is not a routine in the art to isolate, from any organism and man-made library, polynucleotides that encode phosphatidate cytidylyl transferase whose structure is lacking sufficient guidance. Providing the only example of the protein of SEQ ID NO:2 does not provide the guidance as to the structure of the other members of the genus, thus making and using the claimed invention has a low probability of success. In addition, while methods of gene amplification listed under (1)-(8) above are known in the art, the specification fails to guide how to particulary mutate the promoter and regulatory region or ribosome-binding site, extending lifetime of mRNA or preventing degradation of any phosphatidate cytidylyl transferase that is to be used in the methods.

Because of lack of enabling written description the probability of making and using of the invention is low. Examiner concludes that without a further guidance on the part of Applicants in regards to the structure and source of the cdsA genes encoding phosphatidate cytidylyl transferase, as well as the methods of amplification of said proteins, experimentation left to those in the art is improperly extensive and undue.

3. Conclusion

No claim is in condition for allowance.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Malgorzata A. Walicka, Ph.D., whose telephone number is (571) 272-0944. The examiner can normally be reached Monday-Friday from 10:00 a.m. to 4:30 p.m.

If attempts to reach examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy, Ph.D. can be reached on (571) 272-0928. The fax phone number for this Group is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionists whose telephone number is (703) 308-0196.

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Art Unit 1652

Patent Examiner